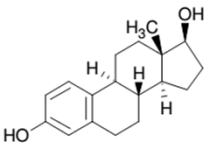
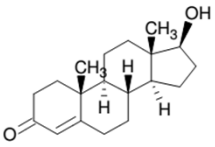
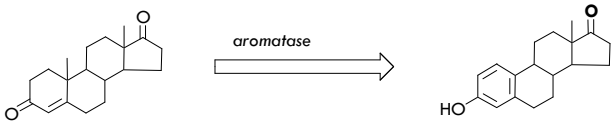


Estradiol
Estra-1,3,5(10)-triene-3,17β-diol



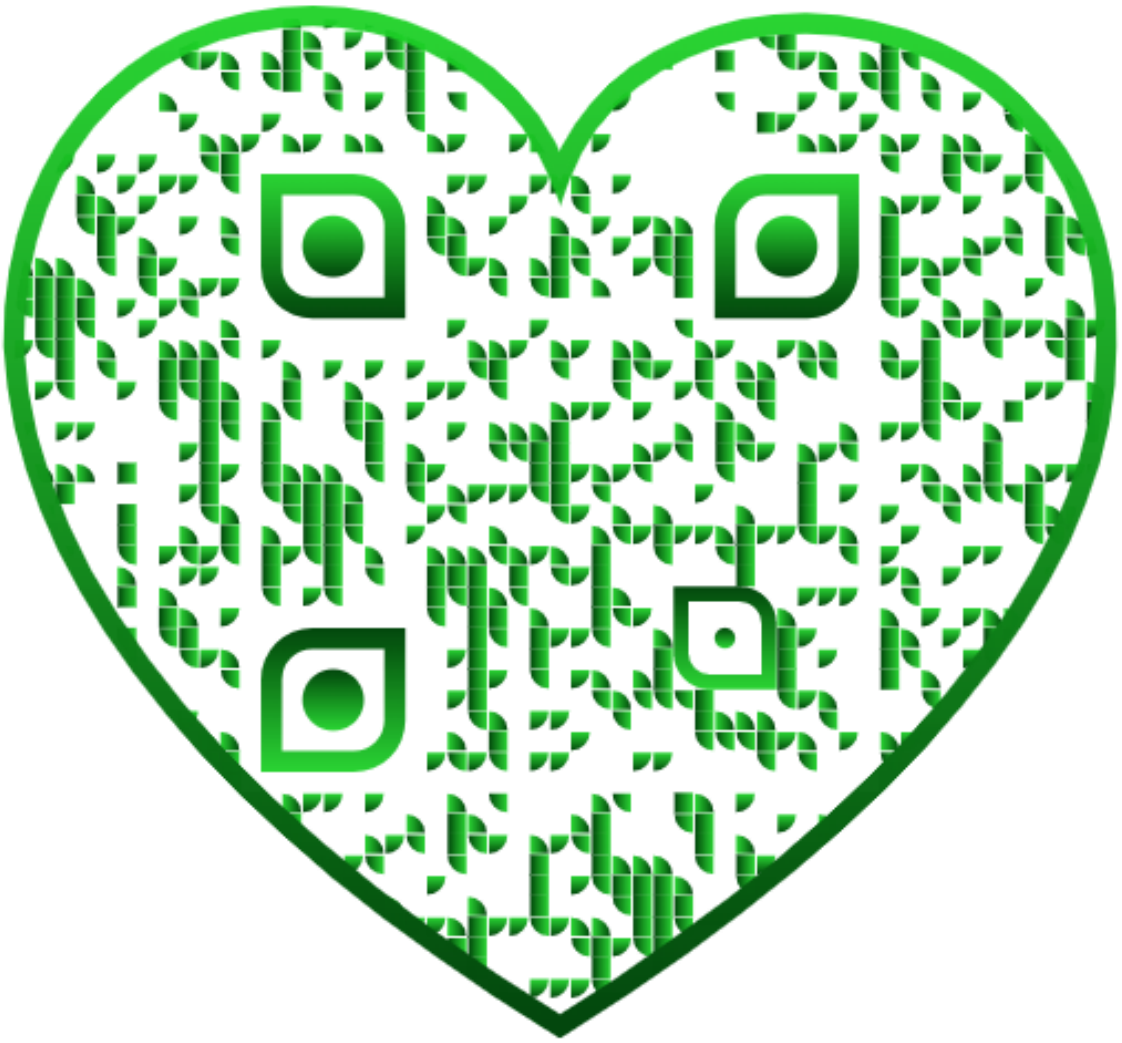
Testosterone
17β-Hydroxyandrost-4-ene-3-one

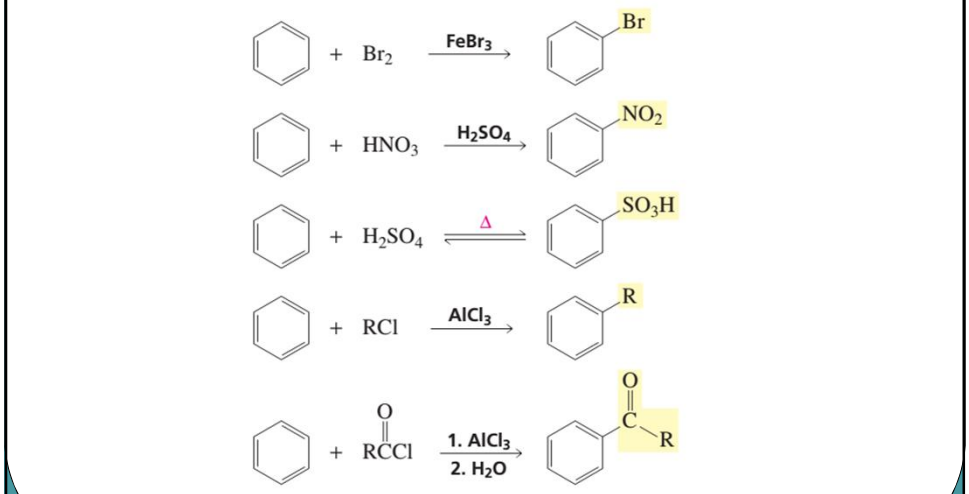


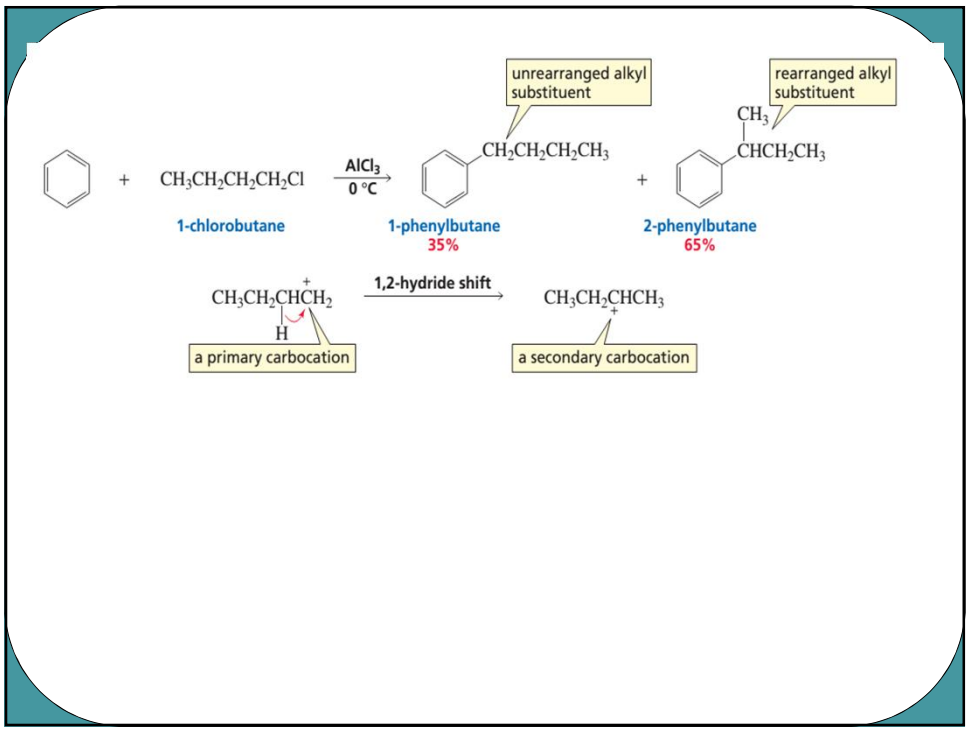
Androstene dione **Estrone**

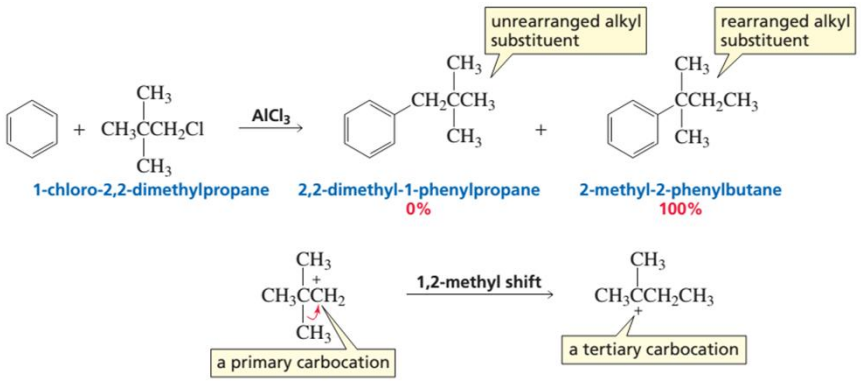
THE TOXICITY OF BENZENE

Although benzene has been widely used in chemical synthesis and has been frequently used as a solvent, it is toxic. Its major toxic effect is on the central nervous system and on bone marrow. Chronic exposure to benzene causes leukemia and aplastic anemia. A higher-than-average incidence of leukemia has been found in industrial workers with long-term exposure to as little as 1 ppm benzene in the atmosphere. Toluene has replaced benzene as a solvent because, although it is a central nervous system depressant like benzene, it does not cause leukemia or aplastic anemia. "Glue sniffers" seek the narcotic central nervous system effects of solvents such as toluene. This can be a highly dangerous activity.




+ Br2
FeBr3
Br
+ HNO3
H2SO4
NO2
+ H2SO4
Δ
SO3H
+ RCl
AlCl3
R
+ RCCl
O
1. AlCl3
2. H2O
O
C
R

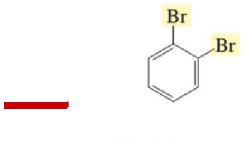

+ CH3CH2CH2CH2Cl
AlCl3
0 °C
1-chlorobutane
CH2CH2CH2CH3
1-phenylbutane
35%
unrearranged alkyl substituent
CH3
CHCH2CH3
2-phenylbutane
65%
rearranged alkyl substituent
CH3CH2CHCH2
H
a primary carbocation
1,2-hydride shift
CH3CH2CHCH3
a secondary carbocation


unrearranged alkyl substituent
rearranged alkyl substituent
AlCl3
1-chloro-2,2-dimethylpropane
2,2-dimethyl-1-phenylpropane
0%
2-methyl-2-phenylbutane
100%
1,2-methyl shift
a primary carbocation
a tertiary carbocation

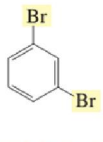
Aromatic halogen compounds

Aromatic halides

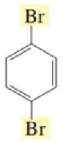
Aryl halides are compounds in which a halogen substituent is attached directly to an aromatic ring (Ar-X) e.g bromobenzene .



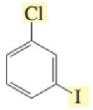
1,2-dibromobenzene
ortho-dibromobenzene
o-dibromobenzene



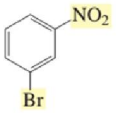
1,3-dibromobenzene
meta-dibromobenzene
m-dibromobenzene



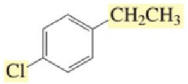
1,4-dibromobenzene
para-dibromobenzene
p-dibromobenzene



1-chloro-3-iodobenzene
meta-chloroiodobenzene
not
1-iodo-3-chlorobenzene or
meta-iodochlorobenzene



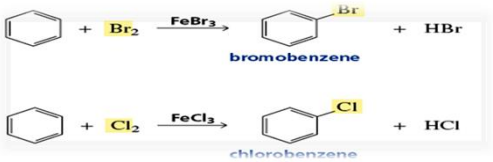
1-bromo-3-nitrobenzene
meta-bromonitrobenzene



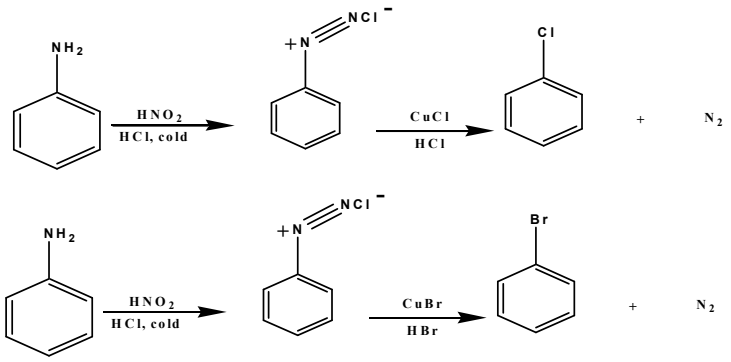
1-chloro-4-ethylbenzene
para-chloroethylbenzene

Methods of preparation

1)Direct halogenation

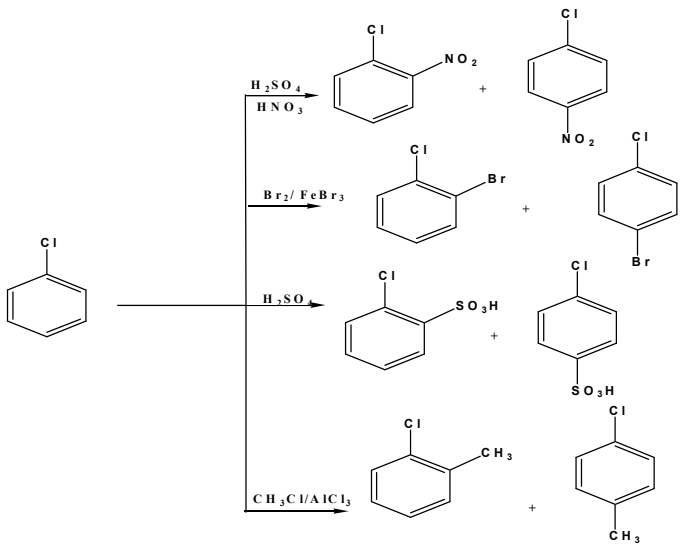


2) Indirect halogenation(from amine)



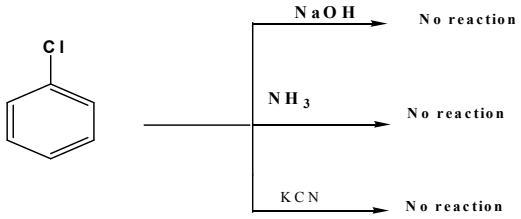
Reactions

Electrophilic aromatic substitution reactions(SE)



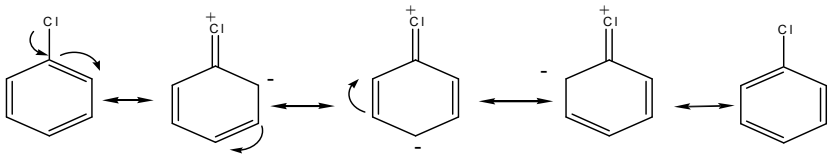
Nucleophilic Reactions:

Unlike alkyl halide ,aryl halides do not undergo Nucleophilic reaction reaily. the halogen bond can not be replaced by OH, NH2, CN with aqueous sodium hydroxide, ammonia or potassium cyanide.



The reason for this unusual lack of reactivity is that C-X in aryl halides is short and strong compared to that in alkyl halides. this is so because

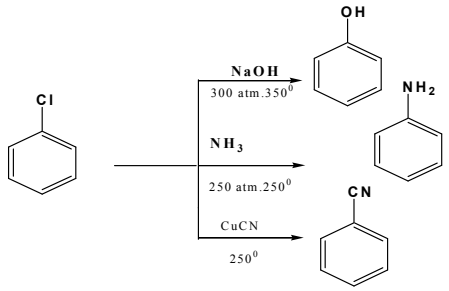
1. The carbon- chlorine bond in chloro benzene has some double bond character as a result of resonance.



2.The aromatic ring with its localized π-electron cloud is considered a center of high electron density.

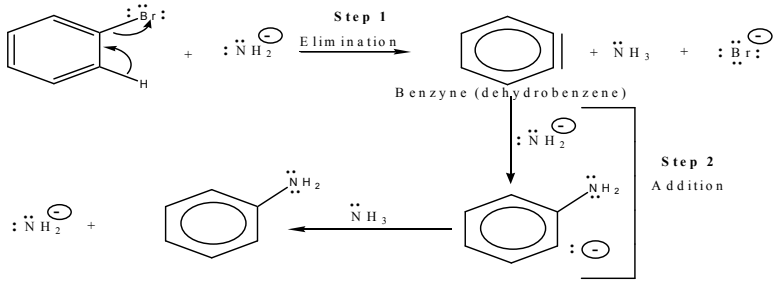
Nucleophilic displacement reactions in aryl halide require drastic or strong conditions to occur.

a)Under drastic conditions: the halogen of an aryl halide can be replaced by an OH, NH2 and CN group when treated with appropriate nucleophilic reagents at high temperature and pressure.(Unimolecular substitution)



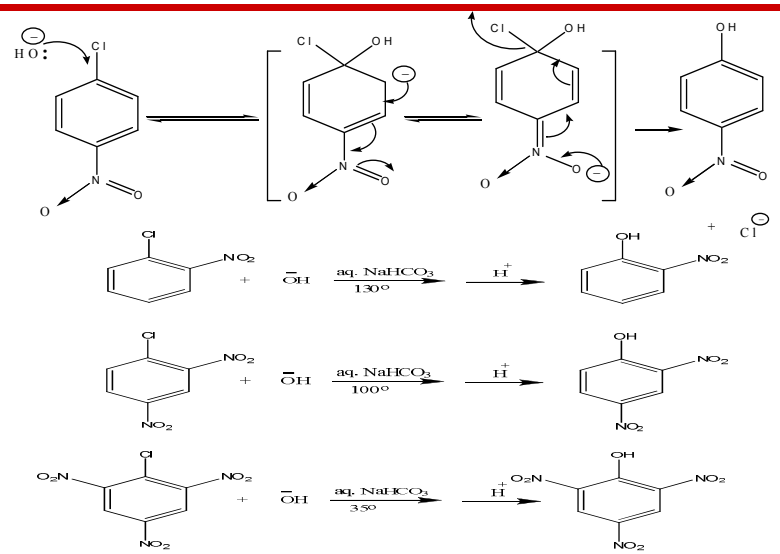
Mechanism

The following elimination -addition mechanism(Benzyne mechanism) is involved:



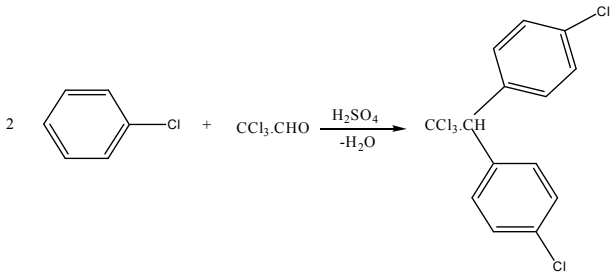
b) The presence of an electron withdrawing groups such as NO2 as second substituent in aryl halide the nucleophilic reaction would take place relatively easily. (Bimolecular substitution).

Explanation:



D.D.T.

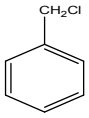
Chlorobenzene is used in the manufacture of D.D.T. by reacting it with chloral in presence of conc sulphuric acid.



The name D.D.T. is a contraction for P, P'- dichlorodiphenyl trichloroethane, . It is a powerful insecticide

The end

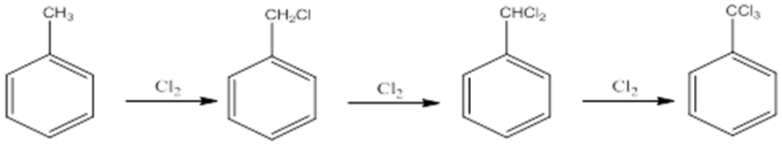
b- Aryl alkyl halides



benzyl chloride

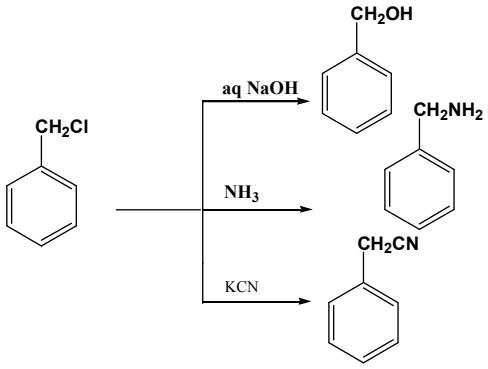
Preparation:

1- Chlorination of boiling toluene, in the absence of catalysts, in sunlight which can produce chlorine atoms and so initiate a chain reaction, gives benzyl chloride, benzylidene chloride (benzal chloride), and benzotrichloride.

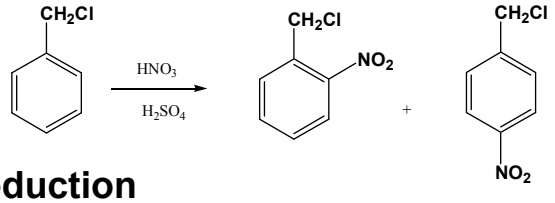


Reactions

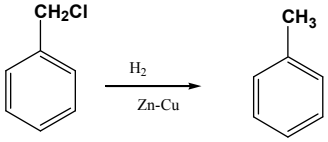
1.Nucleophilic substitution reactions:



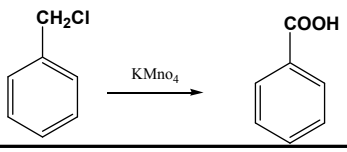
2.Electrophilic aromatic substitution reactions(SE)



3.Reduction

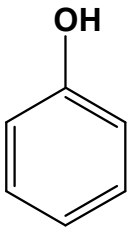


4.Oxidation



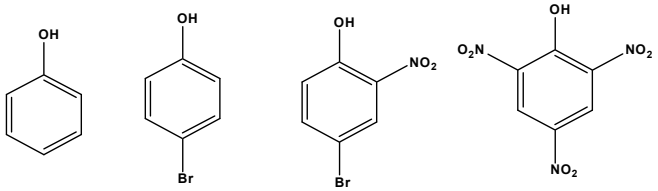
Phenols

phenols are aromatic compounds containing hydroxyl groups directly attached to the nucleus, and they are classified as monohydric, dihydric, trihydric phenols, etc, according as they contain one, two, three, etc hydroxyl group.



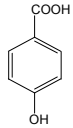
•**Nomenclature:**

1.Numbering of the ring begins at the hydroxyl-substituted carbon and proceeds in the direction that gives the lower number to the next carbon atom bearing a substituent.

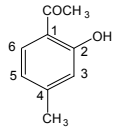


Phenol | p.bromo phenol | 4-bromo-2-nitrophenol | 2,4,6 trinitrophenol

-Carboxyl and acyl groups take precedence over the phenolichydroxyl in determining the base name. The hydroxyl is treated as a substituent in these cases.



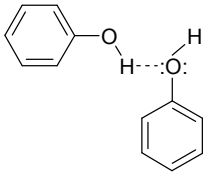
p-hydroxybenzoic acid



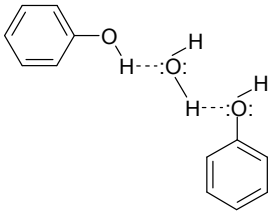
2-hydroxy-4-methylacetophenone

- **Physical properties:**

The physical properties of phenols are strongly influenced by the presenc of the hydroxyl groups which permits phenols to form hydrogen bonds with othe phenol molecules and with water and are more soluble in water than arenes and aryl halides of comparable molecular weight:



A hydrogen bond between two phenol molecules

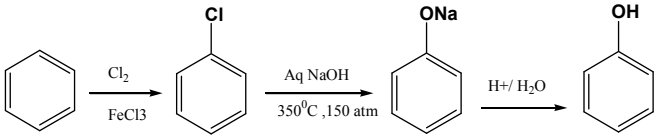


hydrogen bonds between water and phenol molecules

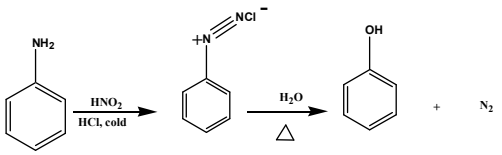
Preparation of Phenols:

The preparation of phenols requires special methods because there is no direct way to introduce -OH group onto an aromatic ring. In laboratory we prepare phenol by

1)Dow process



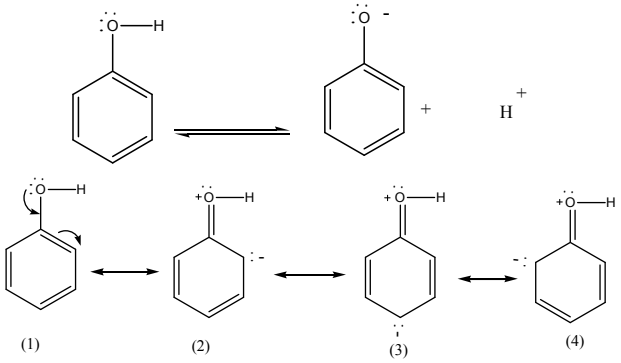
2)Hydrolysis of diazoniume



Acidity of phenols

Phenols are more acidic than alcohols but less acidic than carboxylic acids. Phenol for example will dissolve in aqueous NaOH whereas cyclohexanol will not.

Phenols however, unlike carboxylic acids, do not dissolve in aqueous bicarbonate solution because it is weaker acids than carbonic acid.

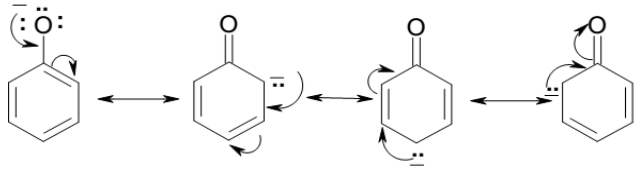


Resonance structure for phenol

The greater acidity of phenols (compared with alcohols) is due to:

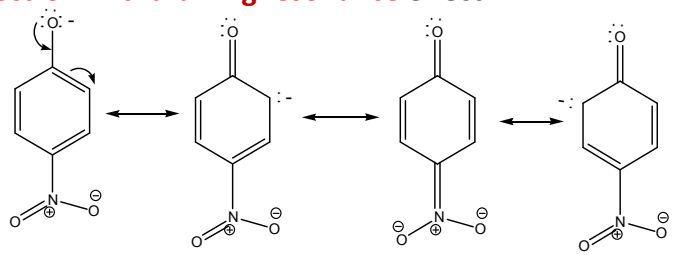
- The electron-withdrawing -I effect of the sp^2 carbon weakens the O-H bond of phenol compared with the effect of the sp^3 carbon of alcohols.

- Resonance stabilization of the phenoxide ion relative to the alkoxide ion: The negative charge on the alkoxide ion $R\text{-}O^-$ (CH_3O^-) can not be delocalized but on phenoxide ion phO^- the negative charge is delocalized to the o- and p- ring positions.



•The election attracting substituents like -X or -NO2 increase the acidity of phenols, and electron releasing substituents like -NH_2 or CH_3 decrease acidity.

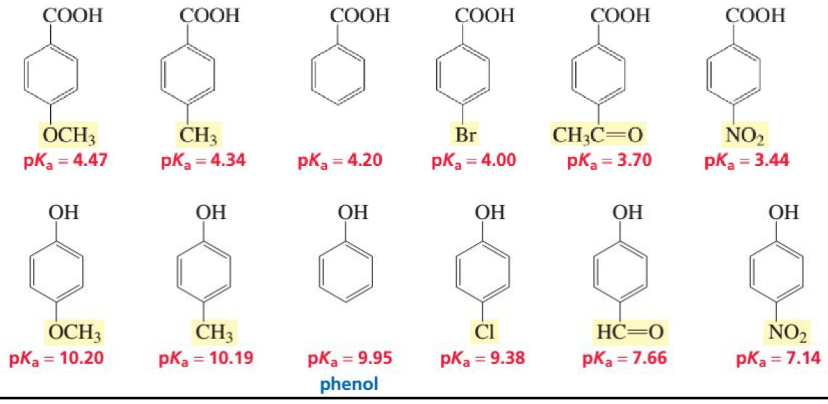
•An ortho and para nitro group greatly stabilizes the phenoxide ion by electron-withdrawing resonance effect.

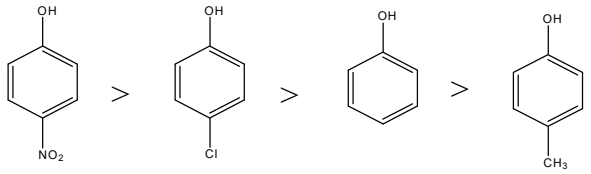


electronegative oxygens of the nitro group accommodate all the negative charge.

The more deactivating (electron withdrawing) the substituent, the more it increases the acidity of a COOH, an OH, or an $^{+}NH_3$ group attached to a benzene ring.

electron withdrawal decreases reactivity toward electrophilic substitution and increases acidity, whereas electron donation increases reactivity toward electrophilic substitution and decreases acidity.





The relative strength of phenols as acids are as follows:

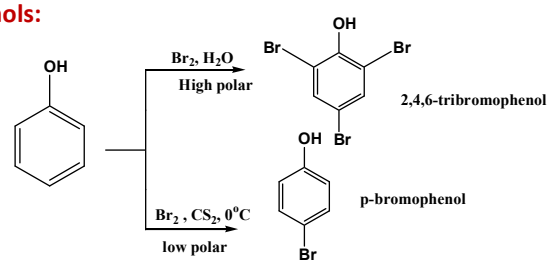
Reactions

phenols undergo electrophilic aromatic substitution reaction much more readily as compare to benzene. The -OH group in phenol is an o- ,p-director and activator.

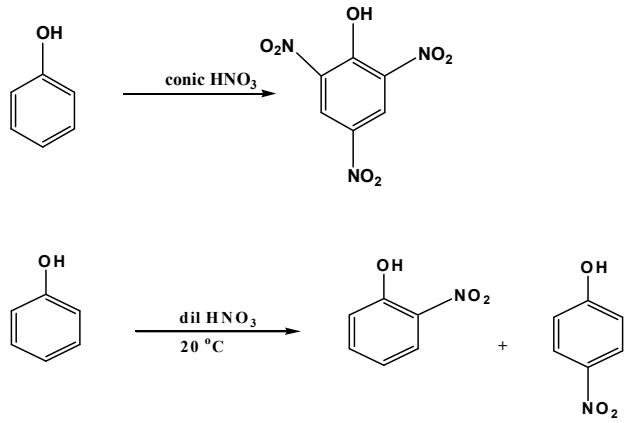
a) Electrophilic aromatic substitution(involving ring)

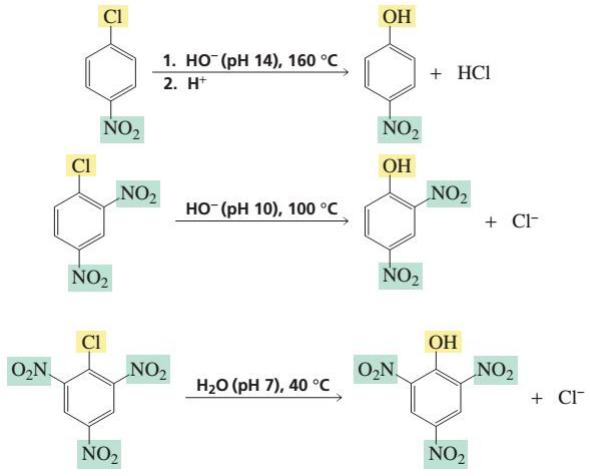
The most chemical property of a phenol is the high reactivity of its ring toward electrophilic substitution.

1. a-Halogenation of phenols:

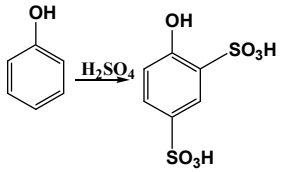


b- Nitration of phenols:

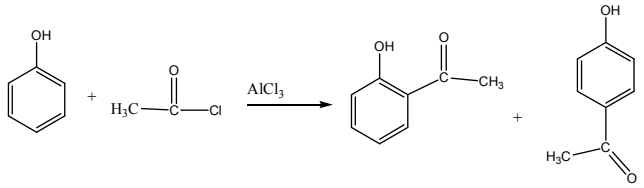




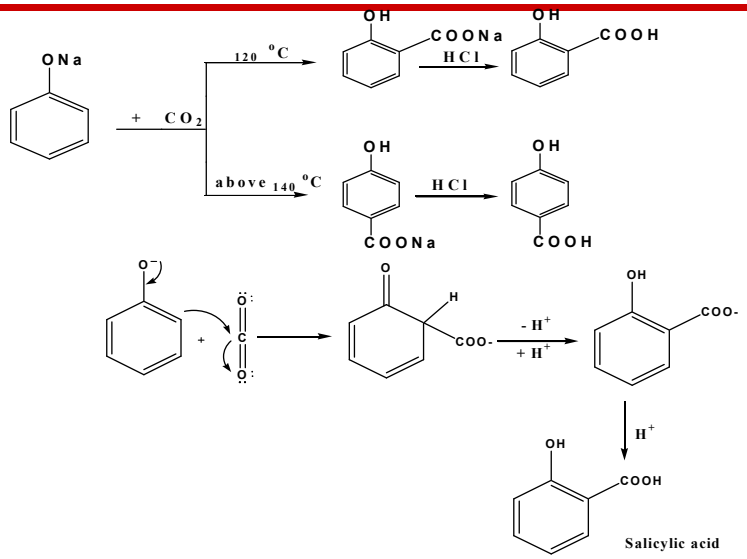
c.Sulphonation of phenol



d.Friedal -craft acylation



e.Carbonation of phenols (Kolbe reaction):

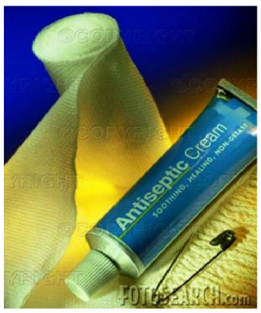


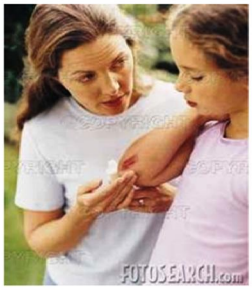
b)Reaction in which the O-H bond is broken.

Esterification

phenol + acetic anhydride ⟶ phenyl acetate

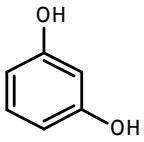
Applications





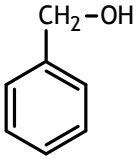
Applications

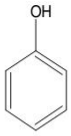
Resorcinol

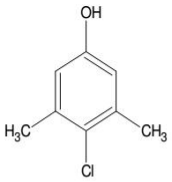


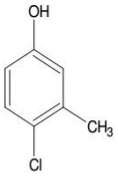
used as Keratolytic in acne,, ringworms, eczema & psoriasis

Benzyl alcohol is used as a preservative in vials of injectable drugs. Also, it has a local anesthetic action



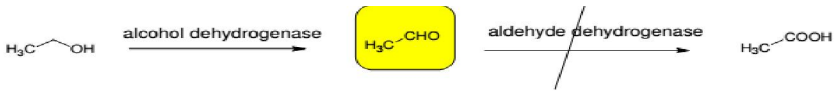






Phenol (Carbolic acid)	*p*-chlorophenol	chloroxylenol	Chlorocresol
(PC = 1) cauteric agent dogs and snake bites	(PC = 3.9) lozenges	(Dettol, PC = 4.8) Topical antiseptic	Phl. preservative

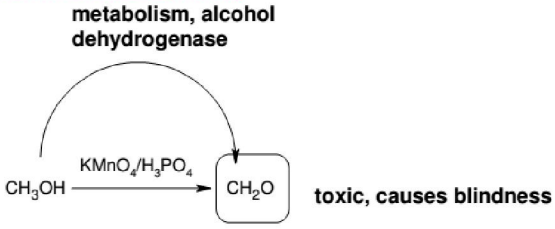
Ethanol $CH_3—CH_2—OH$



- We should test for ***Methanol*** in Ethanol → impurity may cause ***Blindness***.

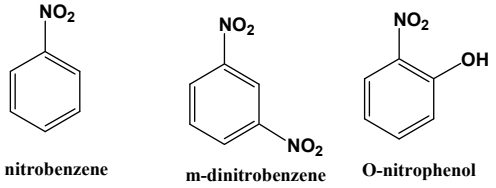
Externally as antiseptic & preservative

Methanol (cause blindness, if ingested):



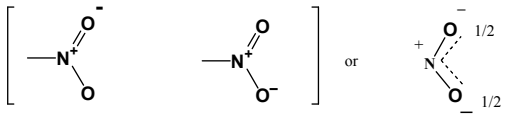
Aromatic nitro compounds

Aromatic nitro compounds are compounds in which one or more nitro groups (-NO2) are attached directly to the aromatic ring

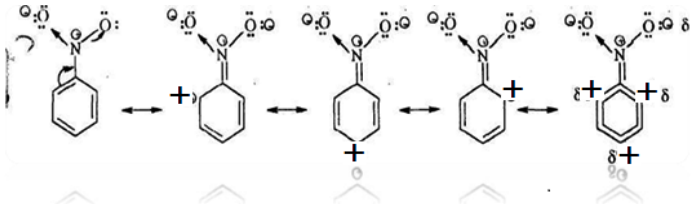


nitrobenzene m-dinitrobenzene O-nitrophenol

The functional group NO2 may be represented by two forms I or II

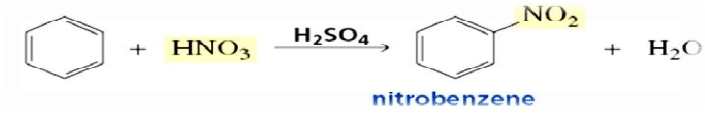


The electronic structure of nitro benzene can be represented as a resonance hybrid having the following

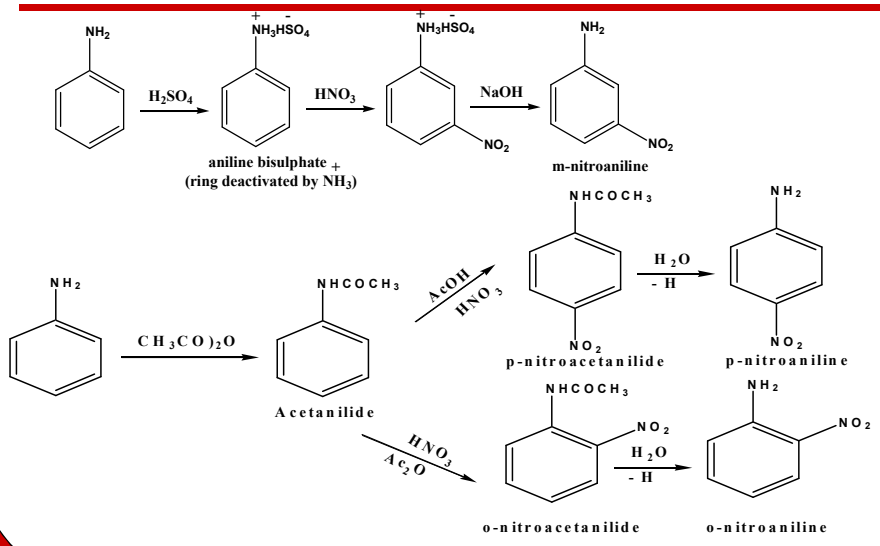


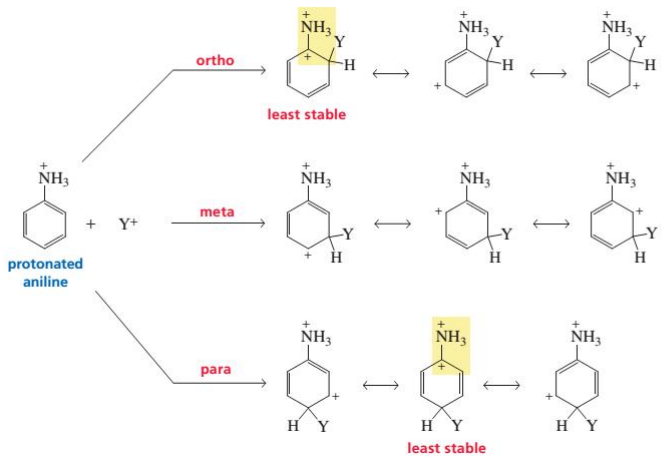
preparation

Aromatic nitro compounds are almost invariably prepared by direct nitration using one of the following reagents;
a- Conc HNO_3
b- Fuming HNO_3
c- Mixed acid: a mixture of HNO_3 (Conc, or fuming) and various amounts of conc. sulphuric acid.



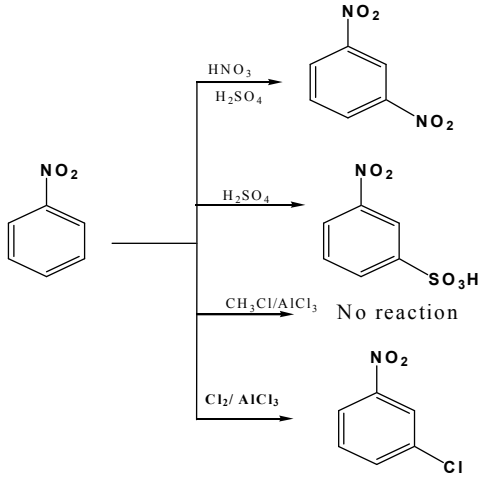
Nitration of aromatic amines:



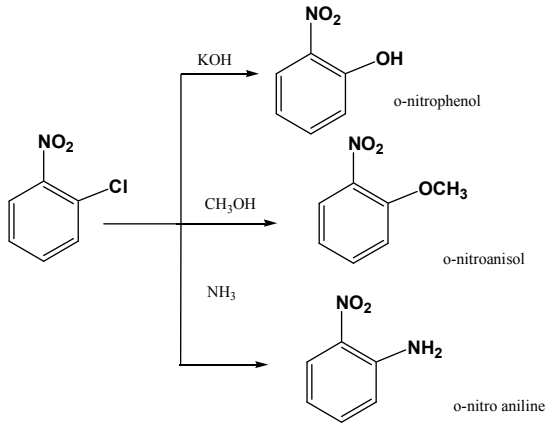


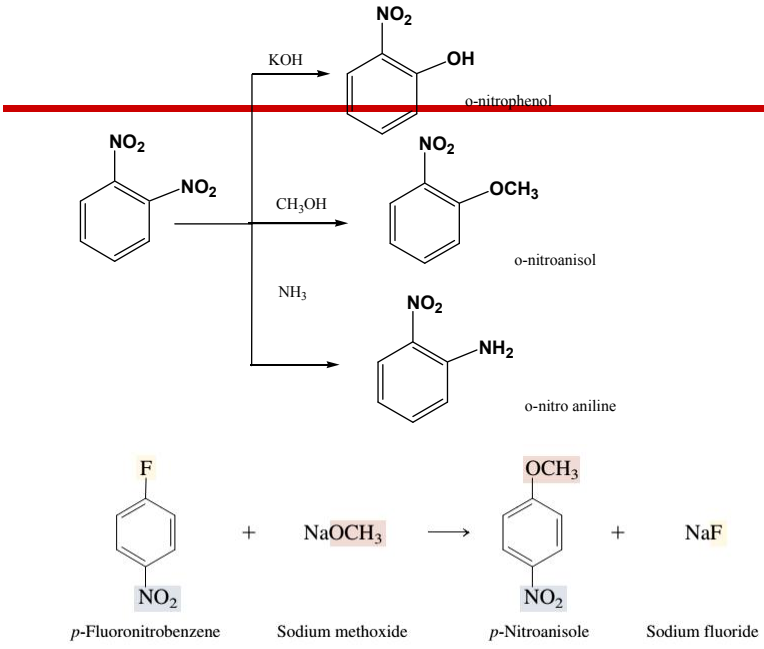
General reactions

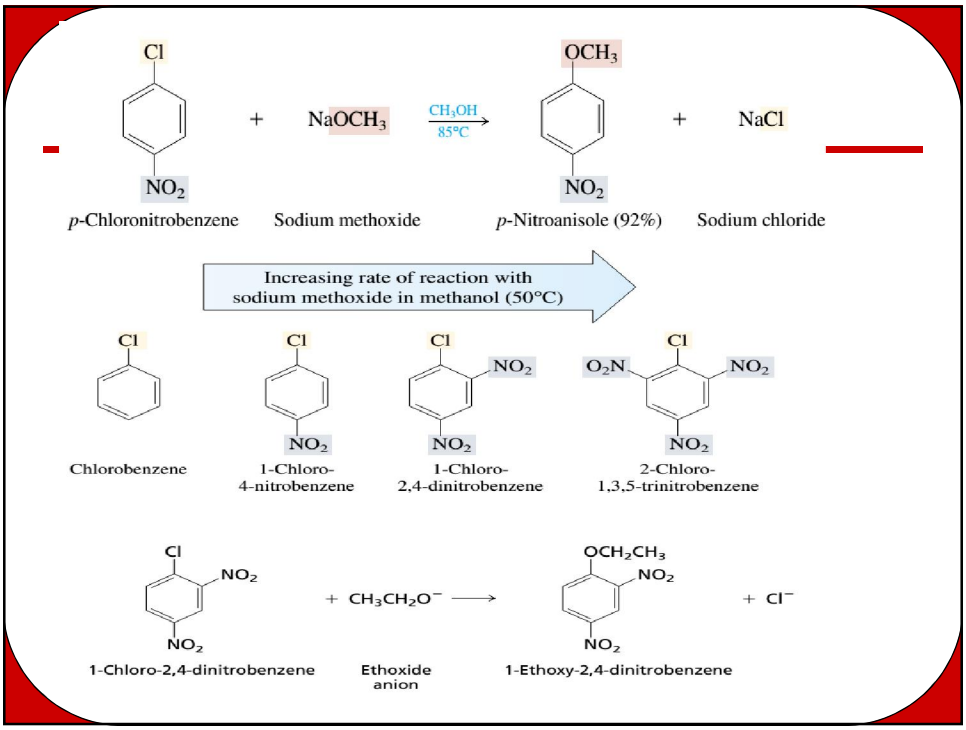
1- Electrophilic substitution:



2- Nucleophilic substitution reaction(SN2)







3.Reduction:

The course of the reduction of nitrobenzene has been shown to take place through primary reduction steps as follows:

$$\text{Ph-NO}_2 \xrightarrow{2H} \underset{\text{Nitrosobenzene}}{\text{PhNO}} \xrightarrow{2H} \underset{\text{N-phenylhydroxylamine}}{\text{Ph-NH-OH}} \xrightarrow{2H} \underset{\text{Aniline}}{\text{PhNH}_2}$$

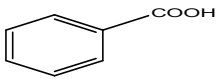
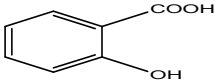
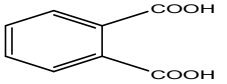
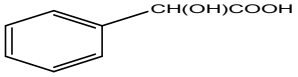
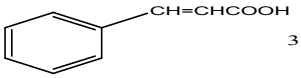
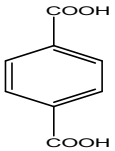
In acid solution (metal and acid): aniline is obtained.

$$\text{Ph-NO}_2 \xrightarrow{\text{Sn/HCl}} \text{PhNH}_2$$

Aromatic Carboxylic acids

Aromatic carboxylic acids are compounds containing one or more carboxyl groups, which are directly attached to the nucleus. Those acids in which the carboxyl group occurs in the side chain may be regarded as aryl substituted aliphatic acids, but they are also classified as aromatic acids, since they exhibit aromatic properties due to the presence of benzene ring.

Nomenclature:

	Systemic name	Common name
	Benzenzcarboxylic acid	benzoic acid
	o-HydroxyBenzenzcarboxylic acid	Salcylic acid
	1,2-Benzenzdicarboxylic acid	Phthalic acid
	2-hydroxy-2-phenylethanoic acid	Mandelic acid
	3-phenylpropenic acid	Cinnamic acid
	1,4-Benzenzdicarboxylic acid	TerPhthalic acid

Physical properties:

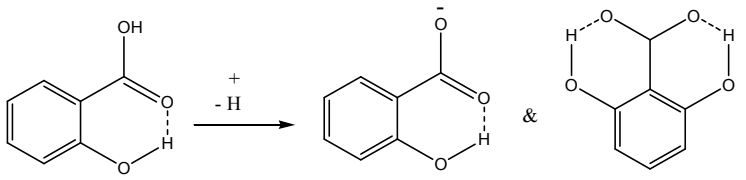
The melting points and boiling points of carboxylic acids are higher than those of alcohols of comparable molecular weight. Carboxylic acids usually form a very unique and strong intermolecular hydrogen bonding . Intramolecular hydrogen bonding in hydroxyacid (e.g., salicylic acid) greatly affects the physical and chemical properties of these acids as shown later

Acidity of Carboxylic Acids :

Carboxylic Acids are more acidic than alcohols and phenols . The high relative acidity of carboxylic acids is attributed to factors which stabilize the carboxylate anion; namely the inductive and the resonance effect of the carbonyl group. Thus, groups that withdraw electrons by inductive effect increases acidity while electron donating groups act in the opposite direction.

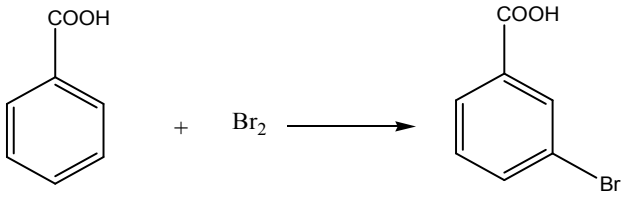
The most pronounced effects are observed when strongly electron-withdrawing substituent at positions ortho to the carboxyl group.

Interestingly, **all ortho substituted benzoic acids** are stronger acids than the corresponding para isomers, regardless of whether the group on the ring is electron-donating or electron-withdrawing. ortho- substituents will "get in the way" of the carboxyl oxygen's unless the latter move out of the plane of the benzene ring, and when this happens the acid weakening resonance effect is greatly diminished (Steric inhibition of resonance).
Intramolecular hydrogen bonding greatly influence the acid strength. Internal hydrogen bonding between the OH and COO^- group of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.



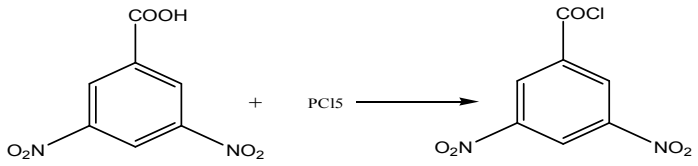
Reactions of carboxylic acids

1- **Electrophilic Substitution:** The carboxyl group is deactivating m-directing group



2-Reactions of the carboxyl group:

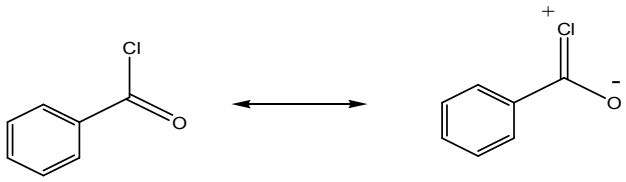
(i) Preparation of Acyl Chlorides: Reagents used are thionyl chloride, phosphorus trichloride, and phosphorus pentachloride,e.g.



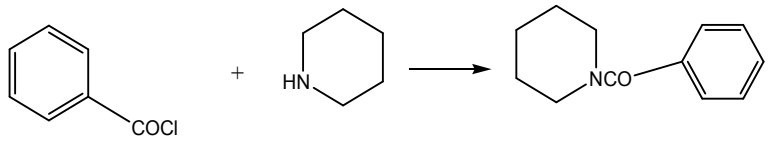
3,5-dinitrobenzoic acid

3,5-dinitrobenzoyl chloride

Acyl chlorides are important intermediates in the preparation of derivatives of carboxylic acids such as acid anhydrides, esters and amides.



The reaction of acyl chloride with an amine in the presence of NaOH is known as **Schotten Baumann reaction**. Example:



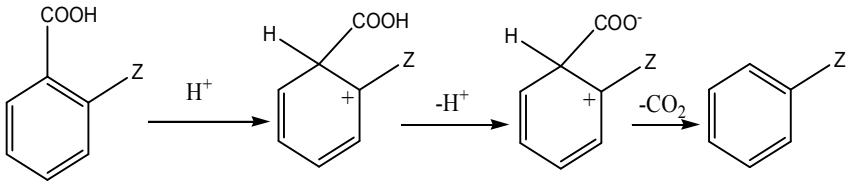
Benzoyl Chloride piperidine N-Benzoyl piperidine

(ii) Preparation of Esters:

1- From acyl chlorides: (e.g. see phenyl esters under phenols).
2- Fischer esterification: In the presence of an acid catalyst alcohols and carboxylic acids react to form esters.

iii) Decarboxylation of Aromatic Acids:

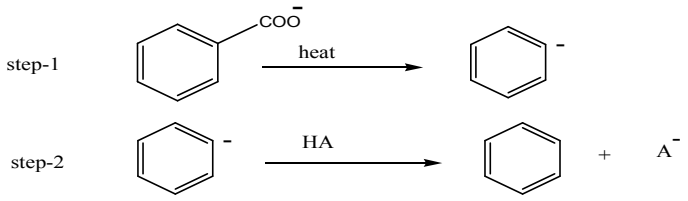
1) **Heating with strong acid:** The reaction is accelerated by the presence of **electron-donating groups in the ortho and para position,** decarboxylation takes place by **the aromatic S_E mechanism** with H^+ as the electrophile and CO_2 as the leaving group



Z= an electron-donating group, e.g., NH_2 group

2) Heating of the carboxylate salt:

In this case **electron withdrawing groups** facilitate the reaction which indicate the formation of a carbanion:



3) heating of the aromatic acid with copper and quinoline

$$ArCOOH \xrightarrow{Cu\ /\ quinoline} ArH + CO_2$$

Preparation:

1)Oxidation of Alkylbenzenes:

One of the most useful methods of preparing aromatic carboxylic acids involves oxidation of alkylbenzenes

$$Ar\text{-}R \xrightarrow{KMnO_4 \text{ or } K_2Cr_2O_7} Ar\text{-}COOH$$

The following observations are important:

•1-In general, a primary or secondary alkyl side chain on aromatic ring is converted to a carboxyl group by the above methods.

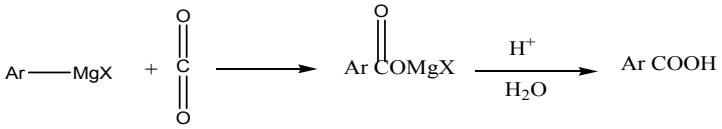
2-Ter. Alkyl group is not susceptible to oxidation under these conditions, because it lacks benzylic hydrogens.

3-It should be noted that substituents such as $-NO_2$, halogen, SO_3H, ArCO-, and -OR are stable under ordinary oxidizing conditions.

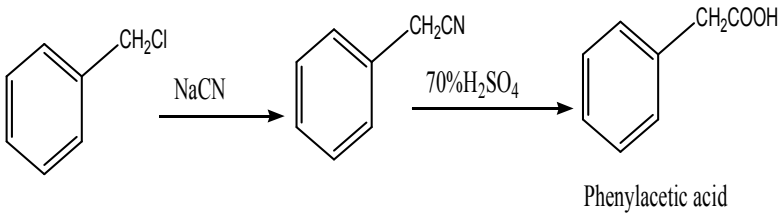
4-Acyl substituents (RCO-) are oxidized to COOH.

5-Hydroxyl and amino substituents render the ring susceptible to oxidation. Compouds containing such groups must first be **protected by acylation** before the oxidation reaction.

2- Carboxylation of Grignard Reagents:



•3-Hydrolysis of Nitriles and cynohydrins

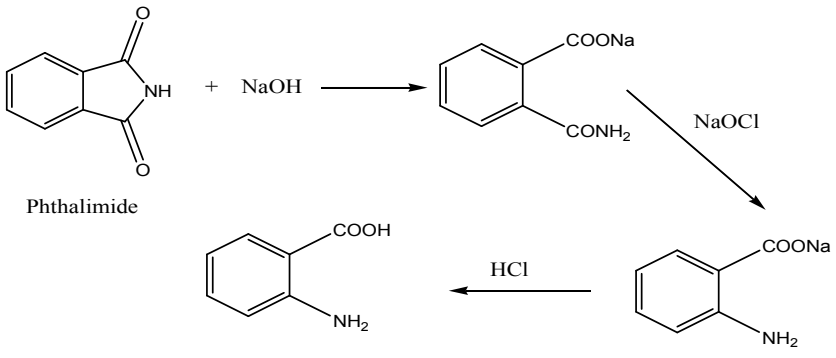


Phenylacetic acid

Some Important Derivatives of AromaticCarboxylic Acids

Anthranilic acid (o-aminobenzoic acid):

It can be prepared by reduction of o-nitrobenzoic acid.
Commercially, it is prepared from phthalimide as follows;



Phthalimide

Important carboxylic acids

Acetic acid (CH_3-COOH) occurs naturally, for example, in vinegar, being produced by bacterial oxidation of ethanol. In its pure form it is called glacial acetic acid. The term glacial arise from the fact that pure acetic acid is a viscous liquid with a melting point of 17 °C. Below 17 °C it solidifies into an ice-looking solid. Acetic acid obtained commercially either by the catalytic oxidation of ethanol, or hydration of acetylene to acetaldehyde followed by oxidation to acetic acid. It is miscible with water yielding an acidic solution.

Benzoic acid (C_6H_5-COOH) is a white crystalline substance with limited solubility in water. Its sodium salt, sodium benzoate (C_6H_5-COONa), is water soluble and can be used as food preservative due to its bactericidal effect.

A number of commonly used drugs are carboxylic acids or carboxylic acid derivatives. Among others, the group of the widely used non-steroidal antiinflammatory drugs (NSAIDs) compromise several carboxylic acid derivatives. The prototype of this group of pharmacologically active compounds is *acetylsalicylic acid* (ASA). Several of the compounds are derivatives of acetic acid, propionic acid or salicylic acid.

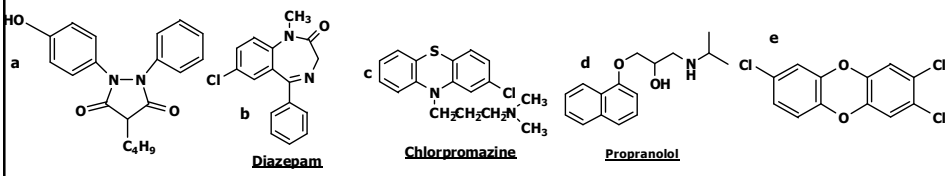
Salicylic acid (SA) and salicylic acid derivatives have complex (antipyretic, antianalgesic and anti-inflammatory) pharmacological effects.

Organic Medicinal Chemistry
Ass Prof Mokhtar Al-Ghorafi

د. مختار الغرافي

Q.3.One ring of the following drugs undergoes oxidation by liver enzymes(metabolism) much more readily than the other?

a) Which one is it ? b) Explain your answer?

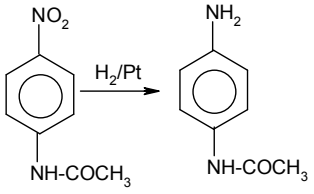


Aromatic amines

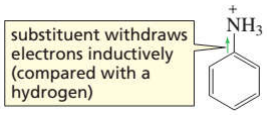
Aromatic amines are of two types, one in which the amino group is attached directly to the ring, and the other in which the amino group is in the side chain. The latter behave very much like the aliphatic amines and so may be regarded as aryl substituted aliphatic amines.

Preparation of Aromatic Amines:

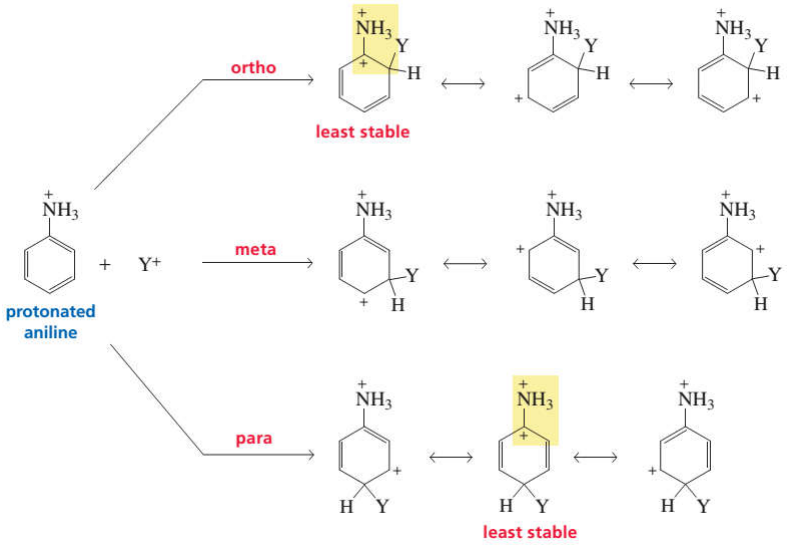
1) From Nitro Compounds:



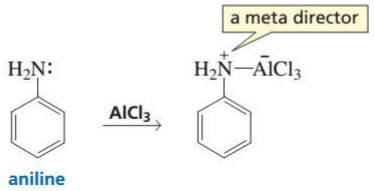
$-\overset{+}{N}H_3$	$-\overset{+}{N}H_2R$	Strongly deactivating
$-\overset{+}{N}HR_2$	$-\overset{+}{N}R_3$	
	$-NO_2$	



If a substituent is *more electron withdrawing than a hydrogen*, it will withdraw the σ electrons away from the benzene ring more strongly than will a hydrogen. Withdrawal of electrons through a σ bond is called **inductive electron withdrawal**. The $^{+}NH_3$ group is a substituent that withdraws electrons inductively because it is more electronegative than a hydrogen.



Aniline and *N*-substituted anilines also do not undergo Friedel–Crafts reactions. The lone pair on the amino group will complex with the Lewis acid ($AlCl_3$) that is needed to carry out the reaction, converting the NH_2 substituent into a deactivating meta director. As we have just seen, Friedel–Crafts reactions do not occur with benzene rings containing meta-directing substituents.

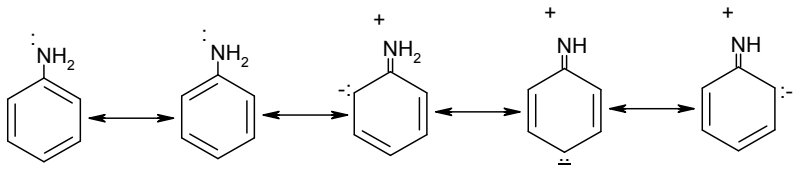


•**Properties and Reactions of Aromatic Amines:**

Basic Properties of Aromatic Amines:

Aromatic amines are basic. Water-insoluble aromatic amines dissolve in aqueous acids forming water-soluble salts.

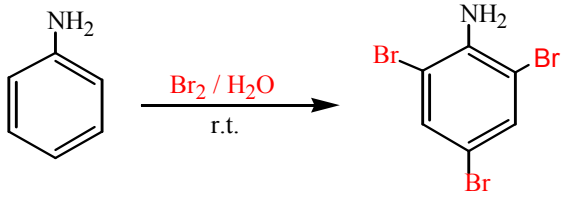
$Ph\text{-}NH_2 + HCl \longrightarrow Ph\text{-}NH_3^+Cl^-$ (aniline HCl)



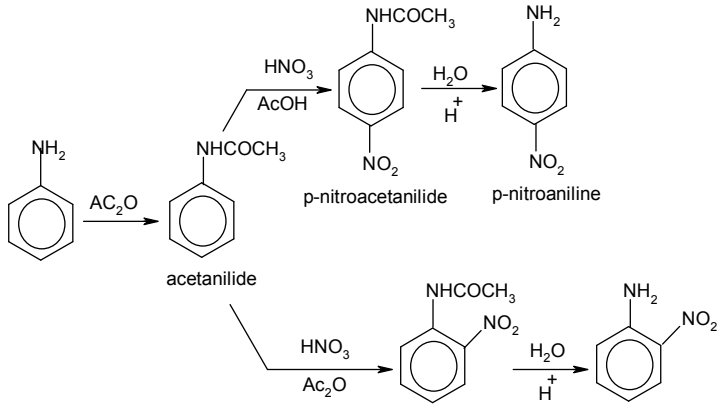
canonical structures of aniline free base)

•**Properties and Reactions of Aromatic Amines:**
Basic Properties of Aromatic Amines:

•**Ring substitution in aromatic amines (S_E reactions):**

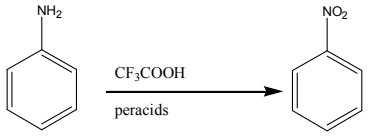


Nitration of Aromatic Amines

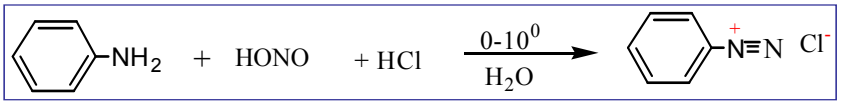


•**Oxidation of aromatic amines**

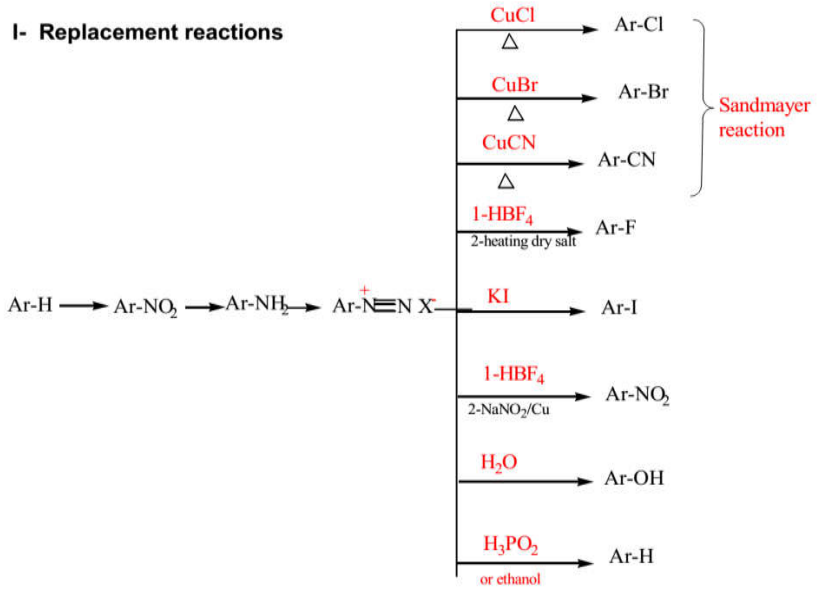
Aromatic amines are sensitive to oxidation.



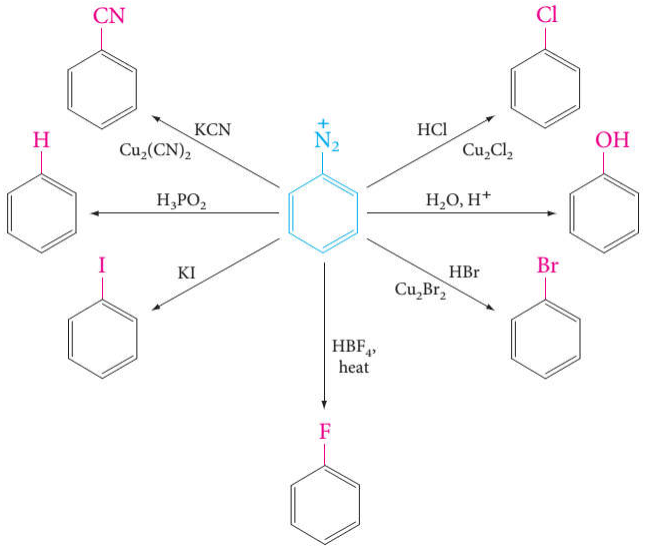
- Reaction with Nitrous acid: Primary arylamines



I- Replacement reactions



Reductive deamination reaction



How can *m*-dibromobenzene be prepared?

Design a route to 1,3,5-tribromobenzene from aniline.